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JSCTT ISSN 2577-1469 JOURNAL OF STEM CELL THERAPY AND TRANSPLANTATION

Opinion

The complement cascade as a target against SARS-CoV-2-induced pneumonia

Gianluigi Ferretti*

IRCCS Regina Elena National Cancer Institute, Division of Medical Oncology 1, Via Elio Chianesi 53, 00144 Rome, Italy

More Information

***Address for correspondence:** Gianluigi Ferretti, MD, PhD, IRCCS Regina Elena National Cancer Institute, Division of Medical Oncology 1, Via Elio Chianesi 53, 00144 Rome, Italy, Email: gianluigi.ferretti@alice.it

Submitted: February 06, 2023
Approved: February 13, 2023
Published: February 14, 2023

How to cite this article: Ferretti G. The complement cascade as a target against SARS-CoV-2-induced pneumonia. J Stem Cell Ther Transplant. 2023; 7: 001-002.

DOI: 10.29328/journal.jsctt.1001029

https://orcid.org/0000-0002-2271-6427

Dear Sir,

Fox, et al. [1] reported on the relevant cardiopulmonary findings in a series of autopsies of patients deceased from SARS-CoV-2 infection. In particular, regarding the histologic examination of the lungs, they observed bilateral diffuse alveolar damage with a lymphocytic infiltrate, thickened alveolar capillaries, fibrin thrombi within the capillaries and small vessels, and entrapment of neutrophils, without any significant neutrophilic, infiltrate within airways or the interstitium.

These findings resemble in part those reported by the Pathology Council of the International Society for Heart and Lung Transplantation (ISHLT) for the diagnosis of cellular-mediated rejection of lung transplant biopsies [2]. According to ISHLT, high-grade cellular-mediated rejection shows diffuse perivascular, interstitial, and air space infiltrates of mononuclear cells, alveolar pneumocyte damage and endothe lialitis, with morphologic evidence of organizing pneumonia, fibrin deposition, or hyaline membranes.

By contrast, the observations reported by Fox, et al. [1] appear in part different from those that, according to the ISHLT, should indicate immunostaining of lung allograft biopsy specimen for complement 4d (C4d) for the diagnosis of antibody-mediated rejection: neutrophilic capillaritis with dense neutrophilic septal infiltrates and fibrin with or without platelet-fibrin thrombi in the microvasculature [2]. Interestingly, even though the role of C4d deposition in the diagnosis of antibody-mediated rejection in lung allografts is still unclear [2], it has been observed that the lung histology in three of five children, after allogenic hematopoietic stem-cell transplant with pulmonary arterial hypertension, showed global thrombotic microangiopathy in the pulmonary arterioles [3].

The efficacy of eculizumab, a humanized monoclonal antibody against the complement component C5, in several patients with transplantation-associated thrombotic micro-angiopathy supports the importance of complement-mediated mechanisms for this clinical entity [4]. The excess in complement activation produces a systemic proinflammatory response to SARS-CoV infection [5] and is associated with significant thrombophilia, with endothelial cell integrity disruption, contributing to thrombotic occlusions in the micro- and even macro-vasculature. Thus, this aberrant complement cascade must be regarded as a crucial therapeutic target in facing SARS-CoV-2-induced pneumonia, as also reported on the activity of an anti-C5a monoclonal antibody in two critical COVID-19 patients [6].

However, it should be considered that different Human Leukocyte Antigen (HLA) molecules are involved in presenting peptides derived from pathogens to T-lymphocytes. It has been reported [7] that triggering an immune reaction and contemporarily being an HLA-DQA1 carrier may induce the production of anti-drug antibodies against anti-TNF drugs, which could represent a tool in the management of COVID-19, thus resulting in their failure against SARS-CoV-2-induced complications.

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